AWARD NUMBER: W81XWH-14-1-0499

TITLE: Characterizing Treatable Causes of Small-Fiber Polyneuropathy in Gulf War Veterans

PRINCIPAL INVESTIGATOR: Anne Louise Oaklander MD, PhD

CONTRACTING ORGANIZATION: Massachusetts General Hospital
Boston, MA 02114

REPORT DATE: October 2017

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

# REPORT DOCUMENTATION PAGE

*Form Approved*
*OMB No. 0704-0188*



| 1. REPORT DATE | 2. REPORT TYPE | 3. DATES COVERED |
|---|---|---|
| October 2017 | Annual | 30 Sep 2016 – 29 Sep 2017 |

**4. TITLE AND SUBTITLE**
Characterizing Treatable Causes of Small-Fiber Polyneuropathy in Gulf War Veterans

**5a. CONTRACT NUMBER**

**5b. GRANT NUMBER**
W81XWH-14-1-0499

**5c. PROGRAM ELEMENT NUMBER**

**6. AUTHOR(S)**
Anne Louise Oaklander MD, PhD
Max M. Klein PhD

E-Mail: aloaklander@mgh.harvard.edu

**5d. PROJECT NUMBER**

**5e. TASK NUMBER**

**5f. WORK UNIT NUMBER**

**7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)**

Massachusetts General Hospital
Boston, MA 02114

**8. PERFORMING ORGANIZATION REPORT NUMBER**

**9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)**

U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

**10. SPONSOR/MONITOR'S ACRONYM(S)**

**11. SPONSOR/MONITOR'S REPORT NUMBER(S)**

**12. DISTRIBUTION / AVAILABILITY STATEMENT**

Approved for Public Release; Distribution Unlimited

**13. SUPPLEMENTARY NOTES**

**14. ABSTRACT**
Damage to the small nerve fibers that sense pain and regulate function of internal organs results in small-fiber polyneuropathy (SFPN). SFPN symptoms include unexplained chronic widespread pain (CWP) and chronic multisymptom illness (CMI) similar to Gulf War Illness. Our prior research demonstrated that SFPN is prevalent in such CWP and CMI syndromes and that it can have onset at a young age. Given these non-specific symptoms, objective testing is recommended for SFPN diagnosis. In the third year of this study Global experts participated in additional rounds of a Delphi process to determine the most reliable markers for SFPN (Case Definition). We also developed a comprehensive database of SFPN patients and well-characterized controls with which to validate the Case Definition. The diagnostic tests recommended under the Case Definition will be applied to Veterans and age-matched controls to look for the prevalence of SFPN.

**15. SUBJECT TERMS**
Neuropathy, Gulf War Illness, chronic widespread pain, chronic multisymptom illness, small-fiber polyneuropathy, case definition

| 16. SECURITY CLASSIFICATION OF: | | | 17. LIMITATION OF ABSTRACT | 18. NUMBER OF PAGES | 19a. NAME OF RESPONSIBLE PERSON |
|---|---|---|---|---|---|
| a. REPORT | b. ABSTRACT | c. THIS PAGE | | | USAMRMC |
| U | U | U | UU | 16 | 19b. TELEPHONE NUMBER *(include area code)* |

**Table of Contents**

**Page**

## 1. INTRODUCTION:

Nerves contain motor, sensory, and autonomic axons, most of which are the small-diameter, unmyelinated C-fibers or thinly myelinated A-delta fibers that sense pain and regulate the function of internal organs and tissues. The farthest ends of these long axons easily malfunction and degenerate if their oxygen, nutrient, or energy supply is compromised, which results in small-fiber polyneuropathy (SFPN). SFPN symptoms include unexplained chronic widespread pain (CWP) and chronic multisymptom illness (CMI), including cardiovascular, gastrointestinal, microvascular, and/or disordered sweating, which contributes to heat and exercise intolerance and fatigue, similar to Gulf War Illness. Given these non-specific symptoms, objective testing is recommended for SFPN diagnosis. Our prior research suggests that SFPN is prevalent in CWP and CMI syndromes [1]. We additionally discovered SFPN that affects adolescents and adults [2]. This early-onset SFPN usually begins in adolescence or early adulthood but can linger to cause CWP and CMI for decades, like Gulf War Illness. Importantly, some causes of early-onset SFPN can be treated and even cured. Our previous preliminary data show that among 38 Gulf War veterans and 41 matched controls, 49% of veterans had objective evidence of SFPN vs. 12% of controls [3]. However, interpretation is uncertain as there is no case definition of SFPN. We recruited a group of global experts and are using validated methods to develop a Case Definition of SFPN. We are validating the selection of Case Definition criteria with an extensive database of patients and well-characterized healthy controls that we developed in the past year. We will then apply this Case Definition in combination with clinical tests, including specific blood tests that we have identified [4] to not only look for the prevalence of SFPN among Gulf War veterans, but also to look for potentially treatable causes.

## 2. KEYWORDS:

Neuropathy, Gulf War Illness, chronic widespread pain, chronic multisymptom illness, small-fiber polyneuropathy, case definition

## 3. ACCOMPLISHMENTS:

### What were the major goals of the project?

**Objective/Hypothesis:**
To determine the prevalence and clinical significance of undiagnosed small-fiber polyneuropathy among Gulf War veterans, and to look for potentially treatable causes of SFPN associated with Gulf War Illness.

**Specific Aims:**

**Aim I:** To develop a working Case Definition of SFPN to help physicians confirm or refute clinically suspected cases and for research use, and then to objectively diagnose the presence or absence of SFPN among Gulf War veteran using validated anatomical and physiological diagnostic tests.

**Aim II:** To perform blood and skin-biopsy tests for the specific treatable causes of SFPN and to compare the prevalence of identified causes in Gulf War veterans with or without SFPN to evaluate the specificity of association.

Within these Specific Aims, three tasks had elements to be performed during the third year of this study. Please note that we obtained permission to extend the period of performance of this study for a fourth year at no cost, in order to continue recruiting study subjects so that we can achieve the necessary significance in our results:

**Task 1. Retrospective analysis and application of Delphi method to develop a Case Definition.** A panel of Experts will contribute benchmark cases through which key health history parameters are used to build the Case Definition.

**Task 2. Apply validated tests to veterans and diagnose SFPN (and controls in Aim II).** Collect evidence pertaining to SFPN from a cohort of 80 veterans and, according to the new Case Definition, screen them for the presence or absence of SFPN in order to establish causality.

**Task 3: Identify treatable causes of SFPN in Gulf War veterans.** Acquire data about the causality of SFPN through tests administered to all subjects to identify abnormal results indicative of SFPN.

**What was accomplished under these goals?**

**Aim I:**

We accomplished the following under Aim I (Task 1):

1. We maintained and improved the Internet site that serves as a secure platform for the Delphi process, which is also a source of information for SFPN patients and researchers. We supplemented the pertinent information on SFPN and added a link to this study as a recruitment tool. The public portion of the website may be accessed at https://NeuropathyCommons.org.

2. We continued to collect responses from the Global experts to two sets of questions, enabling us to narrow the criteria toward a Case Definition of SFPN by applying the Delphi process. The Delphi process is characterized by sets of questions posed to experts who are given an opportunity to modify their responses in successive rounds, until consensus is achieved on the responses. The active list of participating experts is in Appendix 1.

The first set of questions has already undergone two rounds of responses. The second set of questions has undergone a first round of responses, and since most questions in that round are already trending toward consensus, we may not require a second round of responses. The specific questions and results of each round are presented in Appendix 2.

We used these data to draft a Case Definition which we used as the basis for a manuscript that has been provisionally accepted for publication on the efficacy of Intravenous Immunoglobulin for treatment of apparently autoimmune small-fiber neuropathy [5].

3. We created an Access database as a source of clinical cases and research results with which to test the Case Definition. The database consists of patients with diagnoses of small-fiber neuropathy from the electronic medical records of Massachusetts General Hospital, and also healthy controls who have been studied in our laboratory with the same standard tests for neuropathy that we propose as part of the Case Definition. The database currently contains data on 3,495 subjects consisting of 3,087 patients and 408 healthy controls. The prevalence of SFPN can be retrospectively identified while applying the Case Definition. In addition, select cases

from the database can be anonymously uploaded to a REDCap dataset with which the global experts can formally evaluate the Case Definition.

4. Additionally, Dr. Oaklander has been invited to participate in a meeting on small-fiber neuropathy under the ACTTION/ CONCEPPT organization. ACTTION (Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks) is a public-private partnership with the FDA. CONCEPPT (the Consortium on Clinical Endpoints for Peripheral Neuropathy Trials) is a subgroup of ACTTION. These meetings are attended by representatives from academia, FDA, NIH and industry. The primary goal of this meeting is to develop the diagnostic criteria (inclusion and exclusion) for a small-fiber neuropathy clinical trial. Dr. Oaklander's participation will be invaluable in validating our Case Definition.

**Aim II:**

While administering the final rounds of Delphi process questions for developing the Case Definition, we began recruitment of Veterans and age-matched controls for study with the specific tests identified as having the best predictive value for SFPN. We also began retrospective analysis of the cases in our database to validate the selection of criteria within the Case Definition. In the next reporting period we will apply the diagnostic tests with most utility to Gulf War Veterans who are additionally well-characterized by history, skin biopsy, dermatopathology, and autonomic function testing; and to age-matched controls, to look for the prevalence of markers of SFPN that are indicative of causality.

**What opportunities for training and professional development has the project provided?**

Nothing to report. This project is not intended to provide training opportunities. Nonetheless, personnel do gain additional clinical and research skills through their participation.

**How were the results disseminated to communities of interest?**

This project has developed an Internet framework to increase awareness within the affected community and to promote participation in this research project. The website has pages specifically dedicated to patients and their issues, providing resources for information including our research efforts. As such, it will act as an outreach and recruiting tool for Gulf War Veterans among others affected by SFPN.

We also participated in a meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses (the RAC) in April 2017 at which we presented results of our prior studies and progress under our current studies to representatives of Veterans Affairs, researchers, Veterans, and the public.

**What do you plan to do during the next reporting period to accomplish the goals?**

During the next reporting period, we will finalize the Case Definition of small-fiber polyneuropathy (SFPN) via the Delphi method. We will continue to recruit study subjects to include Gulf War Veterans of diverse health histories and normal control volunteers and

combine their studies with retrospective analyses of the cases contained in our database to arrive at a full picture of the prevalence of SFPN and its diagnostic criteria.

## 4. IMPACT:

### What was the impact on the development of the principal discipline(s) of the project?

A goal of this project is to generate a formal Case Definition for small-fiber polyneuropathy which is intended to guide future practice of diagnosticians. Toward that goal, we created a website with public and private Internet pages, to raise awareness of SFPN among Veterans, the general population, and health care professionals through the public pages, and to allow global experts to access the private (secure) pages to answer questions and to add case reports to validate the consensus Case Definition of SFPN.

### What was the impact on other disciplines?

Nothing to report.

### What was the impact on technology transfer?

Nothing to report.

### What was the impact on society beyond science and technology?

As described above, public awareness and attitudes toward SFPN and its sufferers should be impacted by this project.

## 5. CHANGES/PROBLEMS:

### Changes in approach and reasons for change

There have been no changes in our approach, nor are any changes anticipated.

### Actual or anticipated problems or delays and actions or plans to resolve them

It has taken longer to develop the Case Definition as the responses from the Global experts in successive rounds of the Delphi process have taken longer than anticipated. We increased interaction with the Global experts to accelerate consensus on the key parameters of SFPN, and were able to approach consensus on the second set of questions. Although the expert opinions are not yet finalized, the provisional acceptance of a manuscript which applied our draft Case Definition validates our approach and allowed us to proceed with recruitment of study subjects even though not all the tests are defined yet. To accommodate this timeline, we obtained permission to extend the period of performance of this study.

### Changes that had a significant impact on expenditures

Nothing to report.

### Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Nothing to report.

**Significant changes in use or care of human subjects**

Nothing to report.

**Significant changes in use or care of vertebrate animals.**

Not applicable.

**Significant changes in use of biohazards and/or select agents**

Not applicable.

**6. PRODUCTS:**

**Publications, conference papers, and presentations.**

**Journal publications**

Liu X, Treister R, Lang M, Oaklander AL. IVIg for apparently autoimmune small-fiber polyneuropathy: First analysis of efficacy and safety. Provisionally accepted for publication in *Therapeutic Advances in Neurological Disorders*, 2017.

**Website(s) or other Internet site(s)**

The collaboration website for developing the Case Definition continues to be improved and is part of an overall laboratory website that describes small-fiber polyneuropathy, associated research, and resources. It also serves as an effective recruiting tool for Veterans and patients. The site can be accessed at https://NeuropathyCommons.org .

**7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS**

**What individuals have worked on the project?**

| | |
|---|---|
| Name: | Anne Louise Oaklander MD, PhD |
| Project Role: | PI |
| Researcher Identifier (e.g. ORCID ID): | |
| Nearest person month worked: | 2 |
| Contribution to Project: | Dr. Oaklander oversaw updates of the collaboration website and provided content to the website, maintained contact with the International collaborators to participate in developing the Case Definition, and headed the analysis and preparation of the manuscript of IVIg efficacy which initially applied the Case Definition. |
| Funding Support: | No other funding support was used to conduct the work under this award. |

| | |
|---|---|
| Name: | Max Klein PhD |
| Project Role: | Co-Investigator |
| Researcher Identifier (e.g. ORCID ID): | |
| Nearest person month worked: | 3 |
| Contribution to Project: | Dr. Klein maintained IRB and HRPO approval for this project. He also provided content to the collaboration website, advised on the Delphi Method, analyzed Delphi process data, and initiated subject recruitment. |
| Funding Support: | No other funding support was used to conduct the work under this award. |

| | |
|---|---|
| Name: | Stephanie Ortiz BS and Emily Kaiser (replaced Kate O'Neil BS) |
| Project Role: | Clinical Studies Coordinator/Research Assistant |
| Researcher Identifier (e.g. ORCID ID): | |
| Nearest person month worked: | 4 |
| Contribution to Project: | Ms. Ortiz, followed by Ms. Kaiser assisted with maintaining IRB (and HRPO) documentation, contributed content to the collaborative website, and advised on the design of the secure portion of the collaborative website in accordance with the Delphi Method, and assisted with recruitment. |
| Funding Support: | No other funding support was used to conduct the work under this award. |

| | |
|---|---|
| Name: | Heather Downs BS |
| Project Role: | Histotechnologist |
| Researcher Identifier (e.g. ORCID ID): | |
| Nearest person month worked: | 1 |
| Contribution to Project: | Ms. Downs contributed content to the collaborative website including detailed instructions on preparing skin biopsies, processed administrative activities related to this study, and assisted with recruitment. |
| Funding Support: | No other funding support was used to conduct the work under this award. |

**Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**

There are no changes to report that impact personnel effort on this project.

**What other organizations were involved as partners?**

Nothing to report.

## 8. SPECIAL REPORTING REQUIREMENTS

**QUAD CHARTS:** A Quad Chart is provided at Appendix 3.

## 9. REFERENCES


1. Oaklander AL, Herzog ZD, Downs HM, Klein MM. Objective evidence that small-fiber polyneuropathy underlies some illnesses currently labeled as fibromyalgia. *Pain* 2013; 154:2310-2316.
2. Oaklander AL and Klein MM. Evidence of small-fiber polyneuropathy in unexplained, juvenile-onset, widespread pain syndromes. *Pediatrics* 2013;131:e1091-e1100.
3. Oaklander AL and Klein MM. Undiagnosed Small-Fiber Polyneuropathy: Is it a Component of Gulf War Illness? Final Technical Report GW093049, ADA613891, Sept 2014.
4. Lang M, Treister R, Oaklander AL. Diagnostic value of blood tests for occult causes of initially idiopathic small-fiber polyneuropathy. *Journal of Neurology* 2016 Dec;263(12):2515-2527. Epub 2016 Oct 11.

5 Liu X, Treister R, Lang M, Oaklander AL. IVIg for apparently autoimmune small-fiber polyneuropathy: First analysis of efficacy and safety, provisionally accepted for publication in *Therapeutic Advances in Neurological Disorders*, 2017.


## 10. ACRONYMS AND ABBREVIATIONS

ACTTION Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks
AFT Autonomic function test
CMI Chronic multisymptom illness
CONCEPPT Consortium on Clinical Endpoints for Peripheral Neuropathy Trials
CWP Chronic widespread pain
DOD Department of Defense
EMG Electromyography
FDA Food and Drug Administration
HRPO Human Research Protections Office
IRB Institutional Review Board
IVIg Intravenous Immunoglobulin
LEP Laser-evoked potential
MGH Massachusetts General Hospital
NCS Nerve conduction study
NIH National Institutes of Health
PI Principal Investigator
QST Quantitative sensory test
RAC Research Advisory Committee
SFN Small-fiber neuropathy
SFPN Small-fiber polyneuropathy
USAMRMC US Army Medical Research and Materiel Command

**APPENDIX 1. Global experts participating in the Delphi process**

National:

David Herrmann, MD (University of Rochester, Rochester, NY)
Ahmet Höke, MD, PhD (Johns Hopkins Hospital, Baltimore, MD)
Norman Latov, MD, PhD (Weill Cornell Medical College, New York, NY)
Glenn Lopate, MD (Washington University in St. Louis, MO)
Anne Louise Oaklander, MD, PhD (Massachusetts General Hospital, Boston, MA)
A. Gordon Smith, MD (University of Utah, Salt Lake City, UT)

International:

Colin Chalk, MD, CM, FRCPC (McGill University, Montreal, Canada)
Catharina Faber, MD, PhD (Maastricht University Medical Centre, Maastricht, Netherlands)
Alejandra Gonzáles-Duarte, MD (Instituto Nacional de Ciencias Médicas y Nutrició Salvador Zubiran, Tlalpa, Mexico)
Sung-Tsang Hsieh, MD, PhD, MPH (National Taiwan University Hospital, Taipei, Taiwan)
Thierry Kuntzer, MD (Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland)
Giuseppe Lauria, MD (Instituto Carlo Besta, Milan, Italy)
Jean-Pascal Lefaucheur, MD, PhD (Hôpital Henri-Mondor, Public Hospitals of Paris, Paris-Est Créteil University, Créteil, France)
Xiaolei Liu, MD (Dayi Hospital of Shanxi Medical University, Taiyuan, China)
Manoj Menezes, MD (University of Sydney, Children's Hospital, Westmead, Australia)
Osvaldo Nascimento, MD, PhD (Universidade Federal Fluminense, Niterói, Rio de Janeiro, Brazil)
Claudia Sommer, MD (University of Würzburg, Würzburg, Germany)
Judith Spies, MBBS, FRACP, PhD (University of Sydney, Camperdown, Australia)
Thirugnanam Umapathi, MBBS, MRCPE, FAMS (Neurology) (National Neuroscience Institute, Singapore)
Işin Ünal Çevik, MD, PhD (Hacettepe University Faculty of Medicine, Sihhiye-Ankara, Turkey)

Additionally, we finalized the group of leaders that comprise the Scientific Advisory Board to steer the Delphi process. They are:

Verne S. Caviness, Jr., MD, DPhil (Massachusetts General Hospital and Harvard Medical School, Boston, MA) *
Alain Créange, MD, PhD (Hôpital Henri Mondor, Paris Est Créteil, France) *
Peter J. Dyck, MD (Mayo Clinic, Rochester, MN)
John England, MD (Louisiana State University School of Medicine, New Orleans, Louisiana) *
Eva Feldman, MD, PhD (Univ. of Michigan Health System, Ann Arbor, Michigan) *
Riadh Gouider, MD (Razi Hospital, University of Medicine of Tunis, La Manouba, Tunisia) *
Mary M. Reilly, MD, FRCP, FRCPI (University College London, England) *

* also participating as a Global expert in the Delphi process

## APPENDIX 2. Delphi process questions and updated answers in each round

First set of questions and responses for each round so far are as follows (All of the following are out of 23 responses per question in the first round, 10 responses affirming or changing their responses in the second round, and 1 new participant):

1. What name should be used to refer to this illness?

| First round | Second round |
|---|---|
| 6 SFPN (26%) | 4 SFPN (17%) |
| 16 SFN (70%) | 19 SFN (79%) |
| 1 small fiber pathology (4%) | 1 small fiber pathology (4%) |

2. Should we develop criteria for "definite", "probable", and "possible" cases?

| First round | Second round |
|---|---|
| 22 yes (96%) | (not included in the re-vote; no re-vote necessary) |
| 1 no (4%) | |

3. Should this group develop separate diagnostic criteria for clinical vs. research purposes?

| First round | Second round |
|---|---|
| 11 yes (48%) | 10 yes (42%) |
| 12 no (52%) | 14 no (58%) |

4. Which demographic data are important to collect when diagnosing small-fiber (poly)neuropathy? Check all that apply.

| | First round | Second round |
|---|---|---|
| Age | 23 (100%) | 23 (96%) |
| Sex | 23 (100%) | 23 (96%) |
| Race | 17 (74%) | 18 (75%) |
| Ethnicity | 14 (61%) | 17 (71%) |

5. Which diagnostic tests should this group recommend when diagnosing small-fiber (poly)neuropathy? Check all that apply.

| | First round | Second round |
|---|---|---|
| Electromyography (EMG) | 7 (30%) | 6 (25%) |
| Nerve conduction studies (NCS) | 17 (74%) | 18 (75%) |
| Distal leg skin biopsy immunolabeled against PGP9.5 | 21 (91%) | 23 (96%) |
| Quantitative sensory testing (QST) | 12 (52%) | 12 (50%) |
| Somatosensory evoked potentials (SSEP) | 4 (17%) | 4 (17%) |
| Laser evoked potentials (LEP) | 5 (22%) | 4 (17%) |
| Composite autonomic function testing (AFT) | 17 (74%) | 17 (71%) |
| --Heart rate variability during deep breathing | 17 (74%) * | (In this round, the four individual AFT |

| | | |
|---|---|---|
| --Heart rate and blood pressure responses to Valsalva | 17 (74%) * | sub-tests were removed, and only "Composite AFT" was included for clarity) |
| --Heart rate and blood pressure responses to tilt | 17 (74%) * | |
| --Quantitative sweat testing | 17 (74%) * | |

* includes responses that included either the individual sub-test or Composite AFT which includes the individual sub-tests

6. Do you wish to continue to participate?

| First round | Second round |
|---|---|
| 23 (100%) | 24 (100%) |

7. Do you have any conflicts of interest?

| First round | Second round |
|---|---|
| 2 yes (9%) | 2 yes (8%) |
| 21 no (91%) | 22 no (92%) |

7a. Please describe any conflicts of interest.

(One respondent has commercial interest in a company that processes skin biopsies; another has commercial interest in multiple sclerosis treatment and IVIg treatment laboratories)

The second set of questions and first round responses so far are as follows (All of the following are based on 24 respondents per question (as of 6 June 2017)):

"What are the most important parts of the neuro exam to include when examining a patient for possible small-fiber (poly)neuropathy?"

1. Pupils

| | Important | Not important |
|---|---|---|
| Normality of pupil size relative for age and ambient light | 12 (50%) | 12 (50%) |
| Normality of constriction to bright light | 18 (75%) | 6 (25%) |

2. Appearance of lower legs, feet, hands

| | Important | Not important |
|---|---|---|
| Hair loss | 15 (63%) | 9 (38%) |
| Skin hyperperfusion (red, purple, dusky) | 21 (88%) | 3 (13%) |
| Skin hypoperfusion (white, gray) | 18 (75%) | 6 (25%) |
| Edema | 17 (71%) | 7 (29%) |
| Muscle atrophy | 19 (79%) | 5 (21%) |
| High arches | 16 (67%) | 8 (33%) |

| | | |
|---|---|---|
| Hammertoes | 15 (63%) | 9 (38%) |
| Fasciculations | 12 (50%) | 12 (50%) |
| Thin, shiny atrophic skin | 19 (79%) | 5 (21%) |
| Skin excoriations or ulcers (trauma to itchy or painless areas) | 21 (88%) | 3 (13%) |
| Amputations | 20 (83%) | 4 (17%) |

3. Motor function

| | Important | Not important |
|---|---|---|
| Strength of great toe extension | 18 (75%) | 6 (25%) |
| Strength of finger extension | 17 (71%) | 7 (29%) |

4. Sensory function

| | Important | Not important |
|---|---|---|
| Joint position – great toe | 21 (88%) | 3 (13%) |
| 128 Hz vibration – great toe | 21 (88%) | 3 (13%) |
| Light touch – legs, feet, toes | 20 (83%) | 4 (17%) |
| Pin sharpness– legs, feet, toes | 24 (100%) | 0 (0%) |

5. Reflexes

| | Important | Not important |
|---|---|---|
| Ankle jerks as compared to other reflexes such as at knees | 20 (83%) | 4 (17%) |

**APPENDIX 3. Quad Chart**

# Characterizing Treatable Causes of Small-Fiber Polyneuropathy in Gulf War Veterans

GW130109
W81XWH-14-1-0499

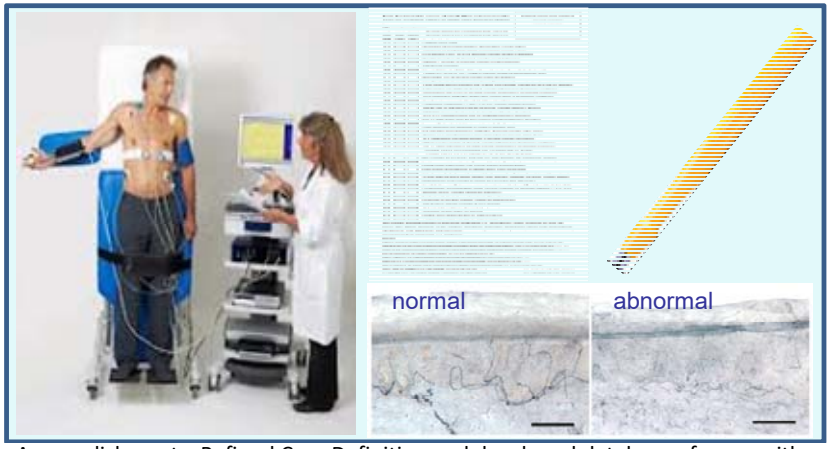
**PI:** Anne Louise Oaklander, MD PhD **Org:** Massachusetts General Hospital **Award Amount:** $1,031,355

## Study/Product Aim(s)

- **Aim I:** To develop a working Case Definition of SFPN, to objectively diagnose the presence or absence of SFPN among Gulf War veteran using validated anatomical and physiological diagnostic tests
- **Aim II:** To perform blood and skin-biopsy tests for the specific treatable causes of SFPN, compare the prevalence of identified causes in Gulf War veterans with or without SFPN

## Approach

Task 1. Retrospective analysis and application of Delphi method to develop a Case Definition.
Task 2. Apply validated tests to veterans and diagnose SFPN (and controls).
Task 3. Identify treatable causes of SFPN in Gulf War veterans.




Accomplishments: Refined Case Definition and developed database of cases with which to test the Definition. Pictured are diagnostics for SFPN: autonomic function test, list of diagnostic blood tests, biopsy punch, skin biopsy slides

## Timeline and Cost

| Activities CY | 14 | 15 | 16 | 17 | 18 |
|---|---|---|---|---|---|
| Task 1. | | | | | |
| Task 2. | | | | | |
| Task 3. | | | | | |
| **Estimated Budget ($K)** | **$57K** | **$344K** | **$344K** | **$287K** | **$0K*** |

* No Cost Extension

**Updated:** 29 October 2017

**Goals/Milestones (Example)**
**CY14 Goal** – Project initiation
☑ IRB and HRPO protocol approval
**CY15 Goals** – Begin Delphi process, identify best tests
☑ Retrospective study of relevant blood tests
☑ Engage Global panel of experts to define SFPN diagnostics
**CY16 – CY17 Goals** – Case definition of SFPN
☑ Develop database of cases
☐ Apply Delphi method, experts validate
**CY17 – CY18 Goals** – Human studies
☐ Collect detailed medical histories
☐ Recruitment, apply validated tests
**Comments/Challenges/Issues/Concerns**
- Slow responses of Global experts, delayed subject recruitment

**Budget Expenditure to Date**
Projected Expenditure: $1,031,355
Actual Expenditure: $902,904